One man’s sorrow, Another man’s hope

- advancement in Brachytherapy for Prostate Cancer

Sep, 2024

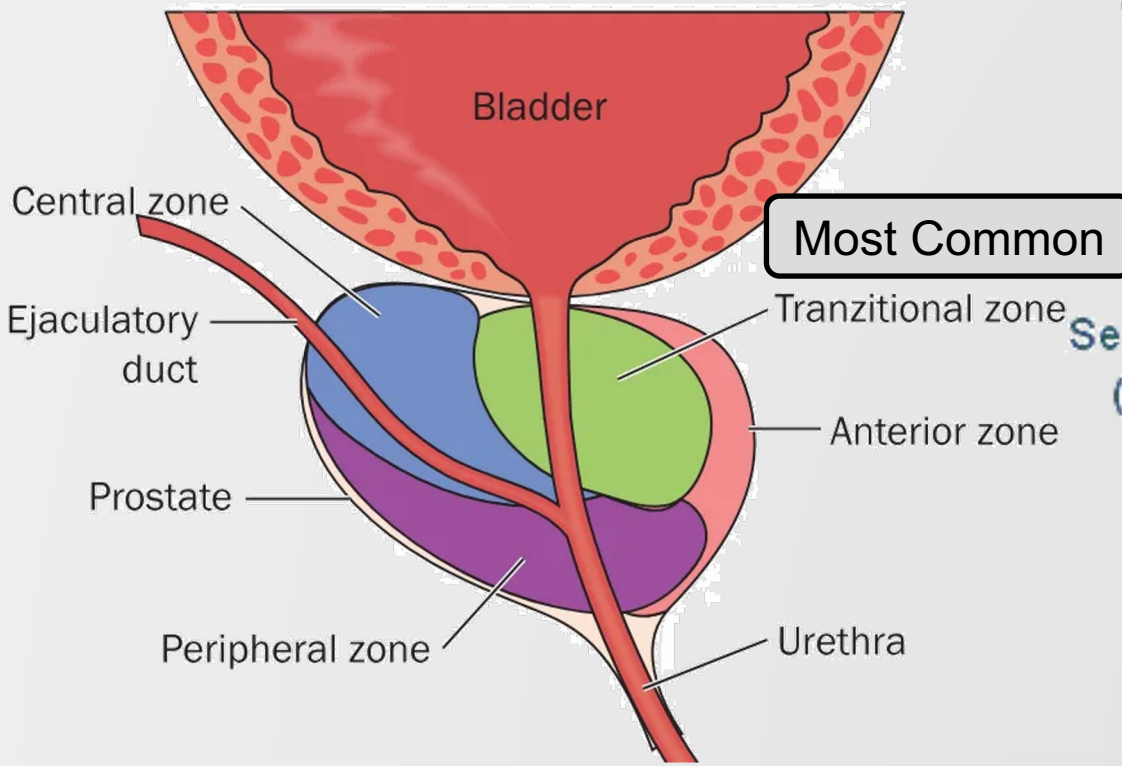
Chengzhu Zhang

Rotation Mentor: Irina Vergalasova

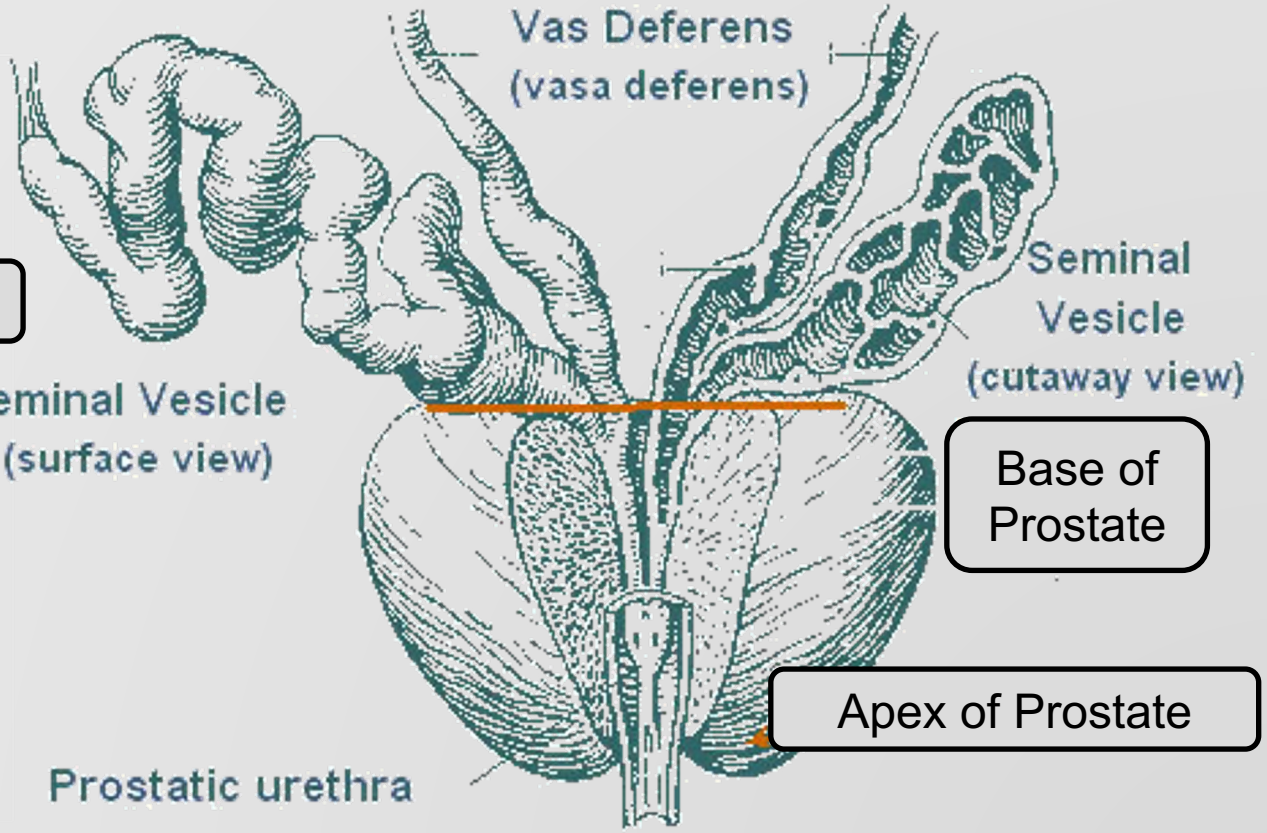
RUTGERS

Prostate anatomy

- In 2021, 3,339,229 new cases were reported in USA.
- Brachytherapy plays a crucial role at the local stage.



Most Common

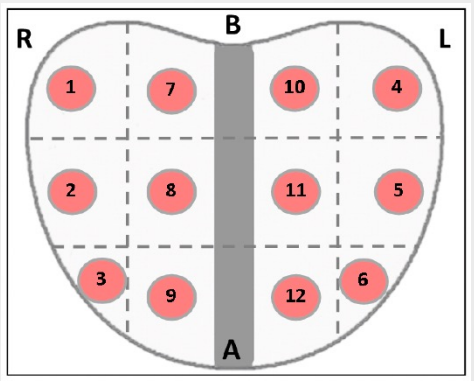


Base of Prostate

Apex of Prostate

Standard Diagnosis for Prostate Cancer

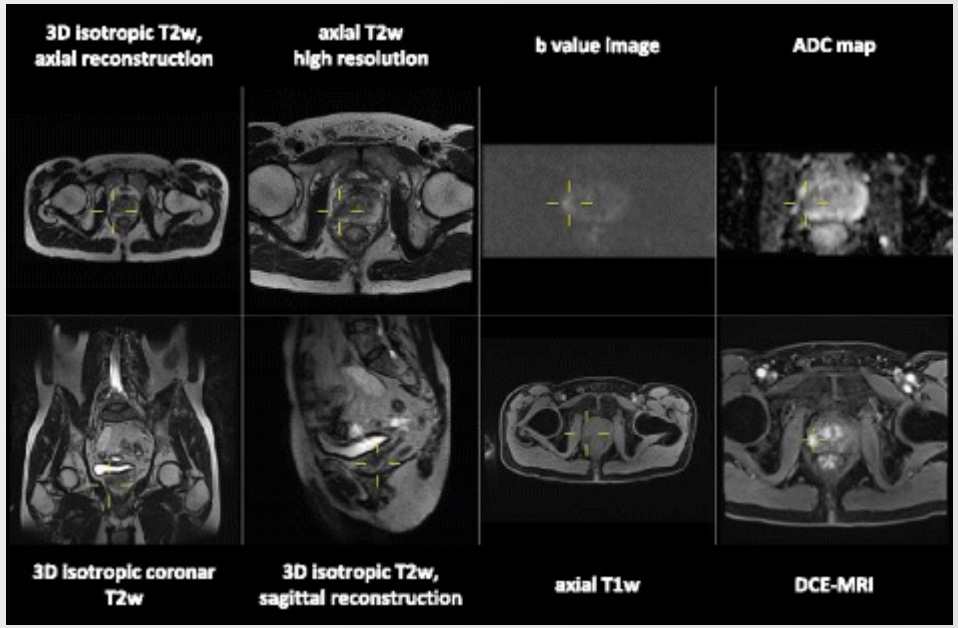
Biopsy



Standard 12 lobes
+ targeted biopsy
(anterior)

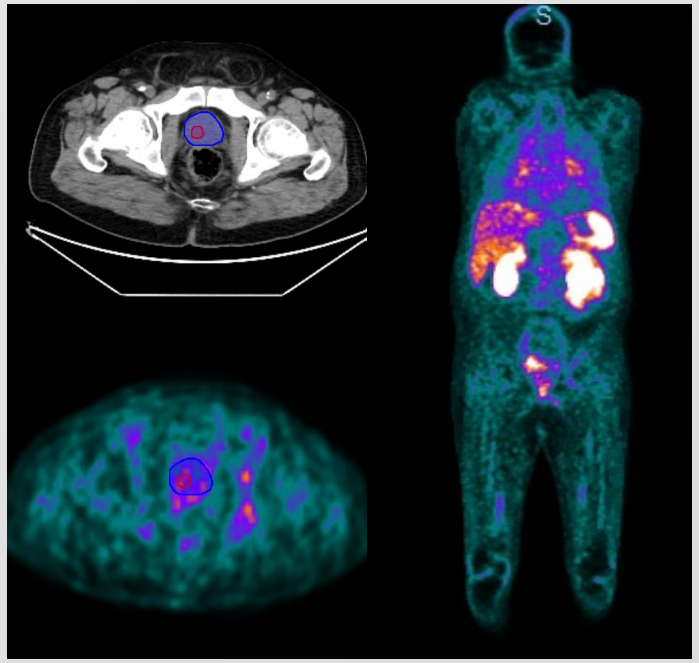
Gleason Score
TNM staging

mpMRI



PI-RADS Category

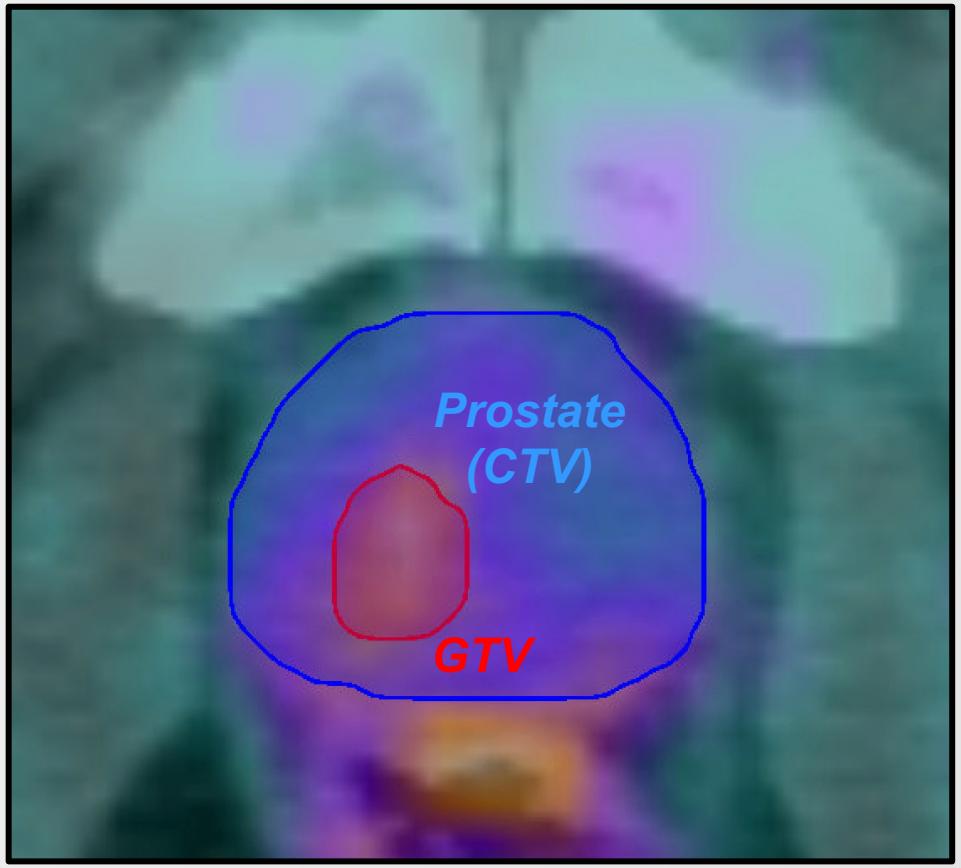
PMSA



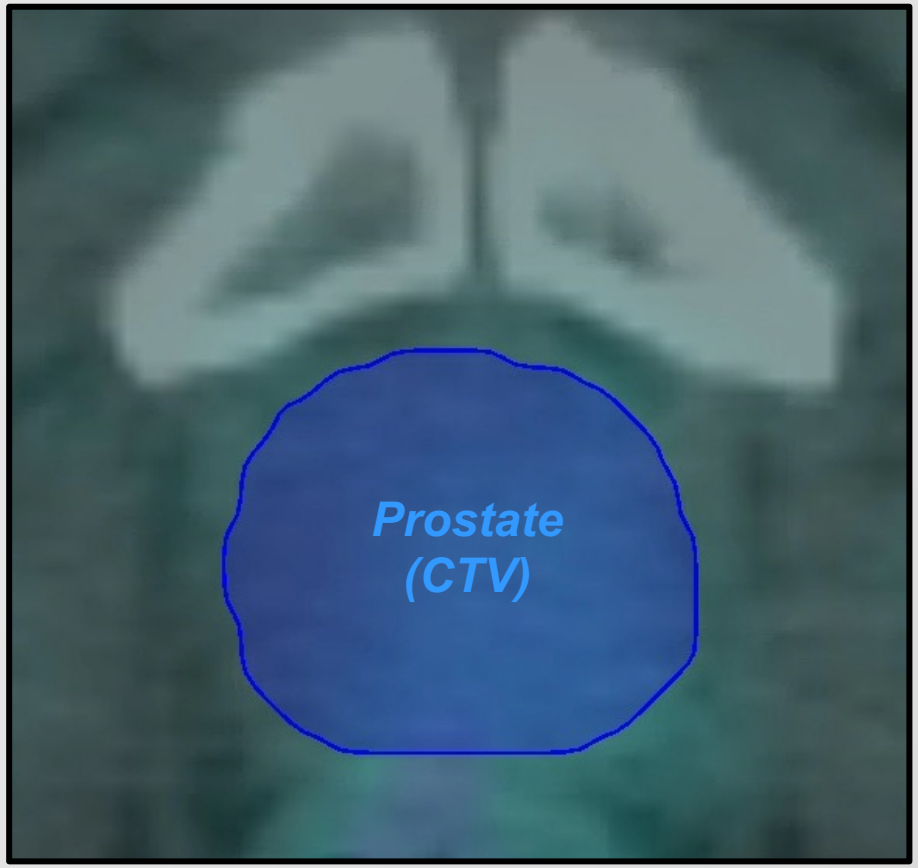
PSA

PSMA: a quantitative biomarker

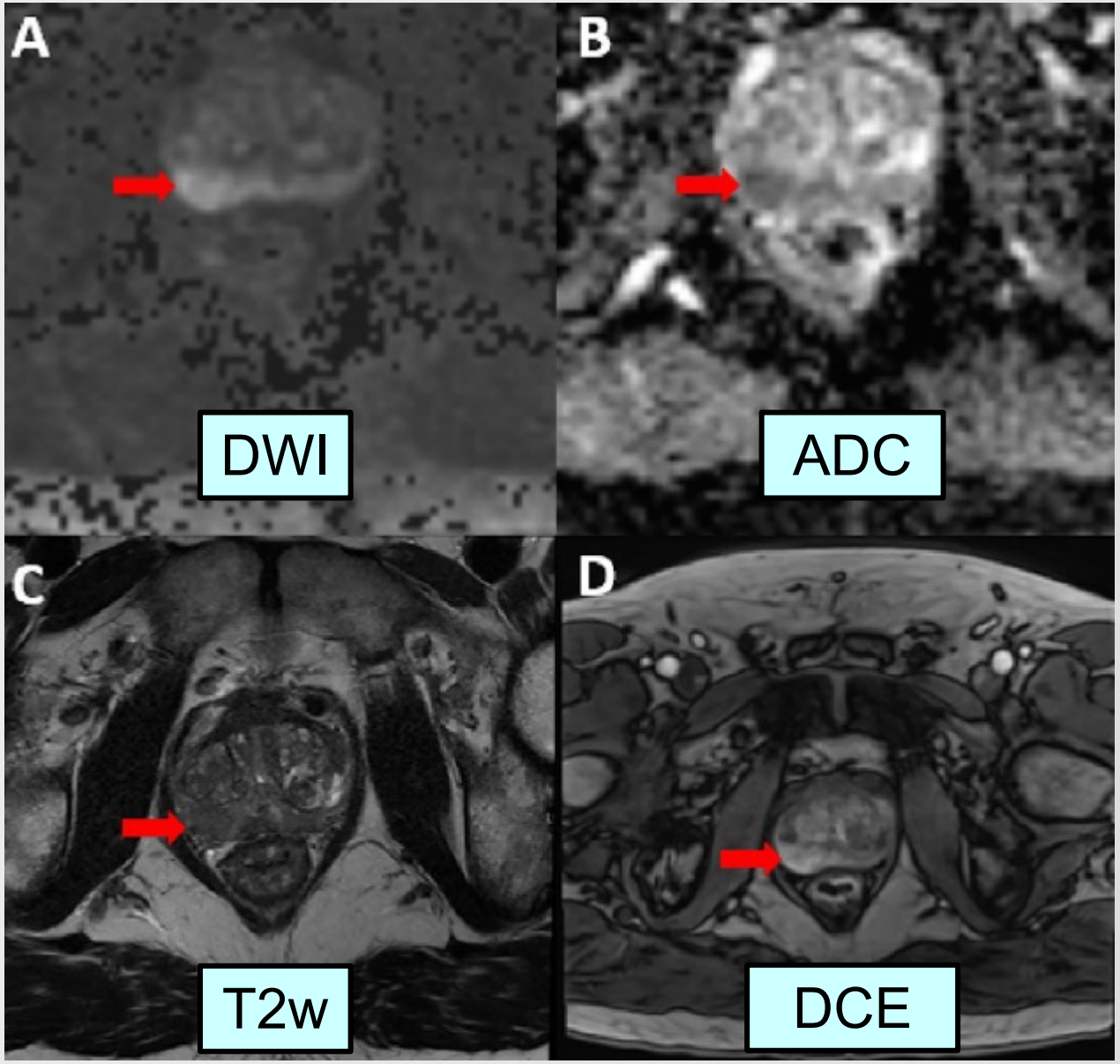
PreOp



Postop



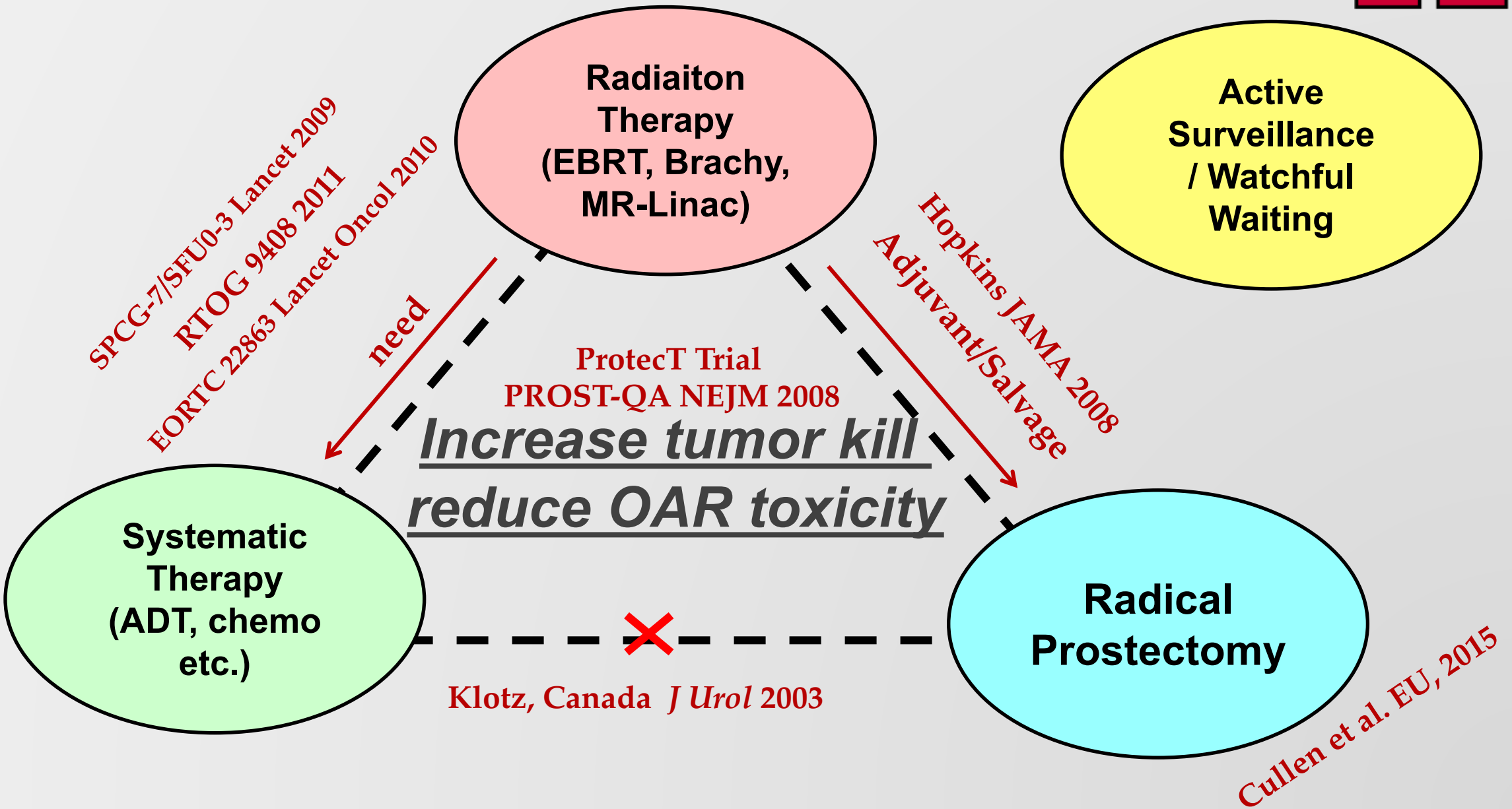
mpMRI: insight into tumor localization



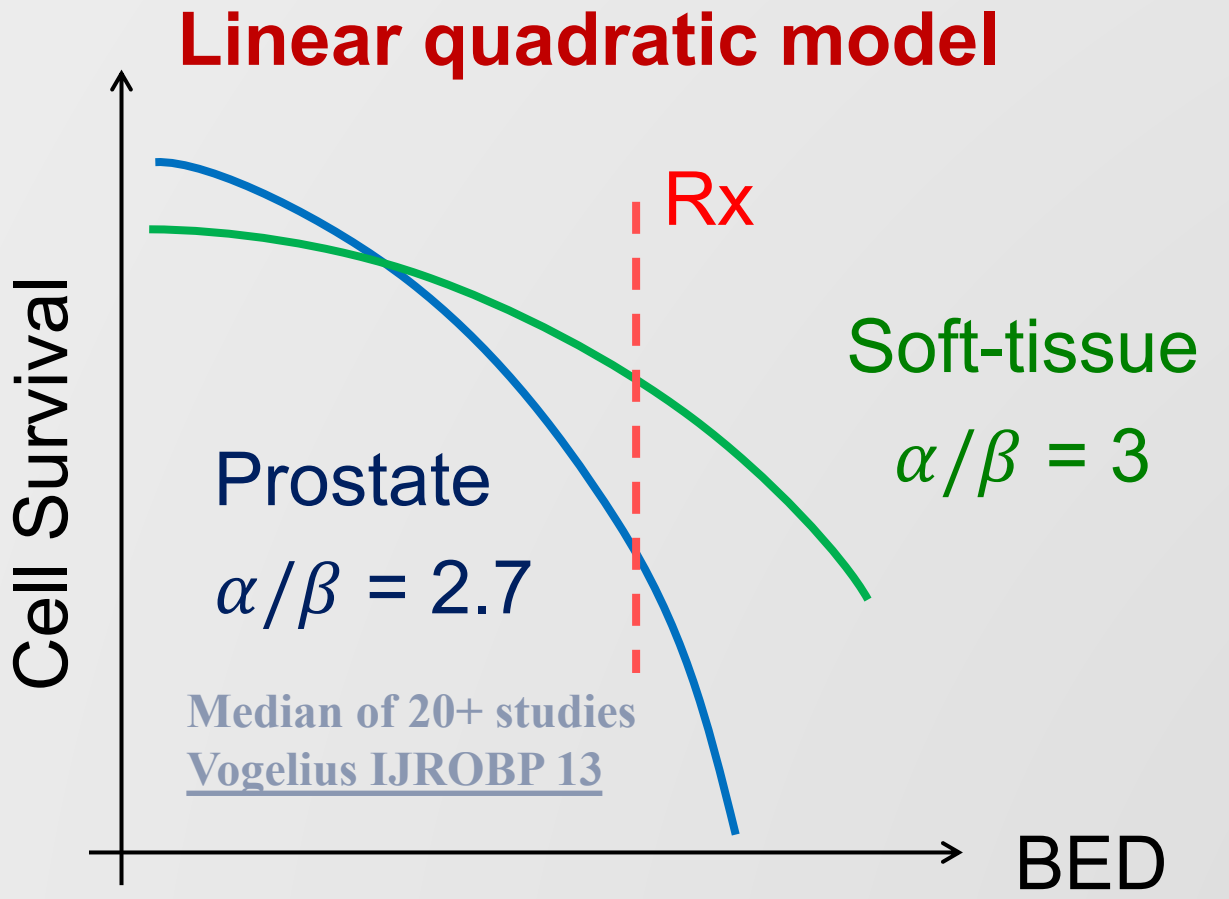
Tumor Staging

<table>
<tr><th colspan="2">Risk Group</th><th colspan="2">Clinical/Pathologic Features (Staging, ST-1)</th></tr>
<tr><td colspan="2">Low-risk Group</td><td colspan="2">• cT1–cT2a
• Grade Group 1
• PSA <10 ng/mL
• ≥3, but <6 prostate biopsy fragments/cores positive</td></tr>
<tr><td rowspan="2">Intermediate</td><td>Favorable</td><td rowspan="2">• No high-risk group features
▸ cT2b–cT2c
▸ Grade Group 2 or 3
▸ PSA 10–20 ng/mL</td><td>• 1 intermediate risk feature
• Grade Group 1 or 2
• <50% biopsy cores positive</td></tr>
<tr><td>Unfavorable</td><td>• >2 intermediate risk features
• Grade Group 3
• ≥ 50% biopsy cores positive</td></tr>
<tr><td colspan="2">High-risk Group</td><td colspan="2">• cT3a –cT4
• Grade Group 4 or Grade Group 5 OR
• PSA >20 ng/mL</td></tr>
</table>

Central aim of treatment to prostate cancer



*Treating pCa from a biophysics perspective



Patient potentially benefits from hypofractionation!

Local control is accompanied by toxicity!

Radiation therapy regimen (NCCN guidelines)

Regimen	Preferred Dose/Fractionation	Low	Favorable Intermediate	Unfavorable Intermediate	High and Very High
EBRT					
Moderate Hypofractionation	3 Gy x 20 fx 2.7 Gy x 26 fx 2.5 Gy x 28 fx	✓	✓	✓	✓
Conventional Fractionation	1.8–2 Gy x 37–45 fx	✓	✓	✓	✓
SBRT Ultra-Hypofractionation	9.5 Gy x 4 fx 7.25–8 Gy x 5 6.1 Gy x 7	✓	✓	✓	✓
Brachytherapy Monotherapy					
LDR Iodine 125 Palladium 103 Cesium 131	140 Gy,145 Gy 125 Gy 115 Gy	✓	✓		
HDR Iridium-192	13.5 Gy x 2 implants 9.5 Gy BID x 2 implants	✓	✓		
Boost Brachytherapy or SBRT with EBRT (2.5 Gy × 15 fx)					
LDR Iodine 125 Palladium 103 Cesium 131	110–115 Gy 90–100 Gy 85 Gy			✓	✓
HDR Iridium-192	15 Gy x 1 fx 10.75 Gy x 2 fx			✓	✓
EBRT + SBRT Boost	9.5 Gy x 2 fx for SBRT boost			✓	✓

Radiation therapy regimen (NCCN guidelines)

Regimen	Preferred Dose/Fractionation	Low	Favorable Intermediate	Unfavorable Intermediate	High and Very High
EBRT					
Moderate Hypofractionation	3 Gy x 20 fx 2.7 Gy x 26 fx 2.5 Gy x 28 fx	✓	✓	✓	✓
Conventional Fractionation	1.8–2 Gy x 37–45 fx	✓	✓	✓	✓
SBRT Ultra-Hypofractionation	9.5 Gy x 4 fx 7.25–8 Gy x 5 6.1 Gy x 7	✓	✓	✓	✓
Brachytherapy Monotherapy					
LDR Iodine 125 Palladium 103 Cesium 131	140 Gy,145 Gy 125 Gy 115 Gy	✓	✓		
HDR Iridium-192	13.5 Gy x 2 implants 9.5 Gy BID x 2 implants	✓	✓		
Boost Brachytherapy or SBRT with EBRT (2.5 Gy × 15 fx)					
LDR Iodine 125 Palladium 103 Cesium 131	110–115 Gy 90–100 Gy 85 Gy			✓	✓
HDR Iridium-192	15 Gy x 1 fx 10.75 Gy x 2 fx			✓	✓
EBRT + SBRT Boost	9.5 Gy x 2 fx for SBRT boost			✓	✓

Radiation therapy regimen: hypofractionation

Regimen	Preferred Dose/Fractionation	Low	Favorable Intermediate	Unfavorable Intermediate	High and Very High
EBRT					
Moderate Hypofractionation	***3 Gy x 20 fx*** 2.7 Gy x 26 fx 2.5 Gy x 28 fx				
Conventional Fractionation	1.8–2 Gy x 37–45 fx				
SBRT Ultra-Hypofractionation	9.5 Gy x 4 fx 7.25–8 Gy x 5 6.1 Gy x 7				
LDR Iodine 125 Palladium 103 Cesium 131	140 Gy,145 Gy 125 Gy 115 Gy				
HDR Iridium-192	13.5 Gy x 2 implants 9.5 Gy BID x 2 implants				
Boost Brach					
LDR Iodine 125 Palladium 103 Cesium 131	110–115 Gy 90–100 Gy 85 Gy				
HDR Iridium-192	15 Gy x 1 fx 10.75 Gy x 2 fx				
EBRT + SBRT Boost	9.5 Gy x 2 fx for SBRT boost				

Is hypo-fractionation effective and safe?

- The potential advantages include improved convenience, *lower cost*. Trials generally show non-inferiority compared to conventional. But toxicity can be higher for some Rx.

Hoffman MDACC (ASTRO 2016)

Dearnaley CHHiP 2016

Lee RTOG 041555

Catton PROFIT

…

Radiation therapy regimen: SBRT

Regimen	Preferred Dose/Fractionation	Low	Favorable Intermediate	Unfavorable Intermediate	High
EBRT					
Moderate Hypofractionation	3 Gy x 20 fx 2.7 Gy x 26 fx 2.5 Gy x 28 fx				
Conventional Fractionation	1.8–2 Gy x 37–45 fx				
SBRT Ultra-Hypofractionation	9.5 Gy x 4 fx 7.25–8 Gy x 5 6.1 Gy x 7				
LDR Iodine 125 Palladium 103 Cesium 131	140 Gy,145 Gy 125 Gy 115 Gy				
HDR Iridium-192	13.5 Gy x 2 implants 9.5 Gy BID x 2 implants				
Boost Brach					
LDR Iodine 125 Palladium 103 Cesium 131	110–115 Gy 90–100 Gy 85 Gy				
HDR Iridium-192	15 Gy x 1 fx 10.75 Gy x 2 fx				
EBRT + SBRT Boost	9.5 Gy x 2 fx for SBRT boost				

Is SBRT effective and safe?

- Biochemical control and toxicity outcomes with SBRT are comparable to historical outcomes of dose-escalated 3D/IMRT.
- Strong non-inferiority evidence shown lately by two phase III trials

HYPO-RT-PC Lancet 2019

PACE-B Lancet Oncol 2019

Radiation therapy regimen: Brachy-monotherapy

Regimen	Preferred Dose/Fractionation	Low	Favorable Intermediate	Unfavorable Intermediate	High
Moderate Hypofractionation	3 Gy x 20 fx 2.7 Gy x 26 fx 2.5 Gy x 28 fx				
Conventional Fractionation	1.8–2 Gy x 37–45 fx				
SBRT Ultra-Hypofractionation	9.5 Gy x 4 fx 7.25–8 Gy x 5 6.1 Gy x 7				
LDR Iodine 125 Palladium 103 Cesium 131	140 Gy,145 Gy 125 Gy 115 Gy				
HDR Iridium-192	13.5 Gy x 2 implants 9.5 Gy BID x 2 implants				
	Boost Brach				
LDR Iodine 125 Palladium 103 Cesium 131	110–115 Gy 90–100 Gy 85 Gy				
HDR Iridium-192	15 Gy x 1 fx 10.75 Gy x 2 fx				
EBRT + SBRT Boost	9.5 Gy x 2 fx for SBRT boost				

Is brachytherapy alone a sufficient treatment?

- The addition of EBRT to brachytherapy did not significantly improve 5-yr progression freedom but did increase late toxicity.

Prestige (LDR)
RTOG 0232
(ASTRO 2016)

Radiation therapy regimen: EBRT+Boost

Regimen	Preferred Dose/Fractionation	Low	Favorable Intermediate	Unfavorable Intermediate	High
Moderate Hypofractionation	3 Gy x 20 fx 2.7 Gy x 26 fx 2.5 Gy x 28 fx	✓	✓	✓	✓
Conventional Fractionation	1.8–2 Gy x 37–45 fx	✓	✓	✓	✓
SBRT Ultra-Hypofractionation	9.5 Gy x 4 fx 7.25–8 Gy x 5 6.1 Gy x 7	✓	✓	✓	✓
Brachytherapy Monotherapy					
LDR Iodine 125 Palladium 103 Cesium 131	140 Gy,145 Gy 125 Gy 115 Gy	✓	✓		
HDR Iridium-192	13.5 Gy x 2 implants 9.5 Gy BID x 2 implants	✓	✓		
Boost Brachytherapy or SBRT with EBRT (2.5 Gy × 15 fx)					
LDR Iodine 125 Palladium 103 Cesium 131	110–115 Gy 90–100 Gy 85 Gy			✓	✓
HDR Iridium-192	15 Gy x 1 fx 10.75 Gy x 2 fx			✓	✓
EBRT + SBRT Boost	9.5 Gy x 2 fx for SBRT boost			✓	✓

Radiation therapy regimen: Brachytherapy boost

Regimen	Preferred Dose/Fractionation	Low	Favorable Intermediate	Unfavorable Intermediate	High
Moderate Hypofractionation	3 Gy x 20 fx 2.7 Gy x 26 fx 2.5 Gy x 28 fx				
Conventional Fractionation	1.8–2 Gy x 37–45 fx				
SBRT Ultra-Hypofractionation	9.5 Gy x 4 fx 7.25–8 Gy x 5 6.1 Gy x 7				
LDR Iodine 125 Palladium 103 Cesium 131	140 Gy,145 Gy 125 Gy 115 Gy				
HDR Iridium-192	13.5 Gy x 2 implants 9.5 Gy BID x 2 implants				
	Boost Brach				
LDR Iodine 125 Palladium 103 Cesium 131	110–115 Gy 90–100 Gy 85 Gy				
HDR Iridium-192	15 Gy x 1 fx 10.75 Gy x 2 fx				
EBRT + SBRT Boost	9.5 Gy x 2 fx for SBRT boost				

Can brachytherapy boost improve outcomes in addition to EBRT?

- Brachytherapy boost, i.e. replacing part of EBRT fx, is associated with increased toxicity but may benefit higher risk pts.

Morris
ASCENDE-RT
(IJROBP 2016)

Radiation therapy regimen: SBRT boost

Regimen	Preferred Dose/Fractionation	Low	Favorable Intermediate	Unfavorable Intermediate	High
Moderate Hypofractionation	3 Gy x 20 fx 2.7 Gy x 26 fx 2.5 Gy x 28 fx				
Conventional Fractionation	1.8–2 Gy x 37–45 fx				
SBRT Ultra-Hypofractionation	9.5 Gy x 4 fx 7.25–8 Gy x 5 6.1 Gy x 7				
LDR Iodine 125 Palladium 103 Cesium 131	140 Gy,145 Gy 125 Gy 115 Gy				
HDR Iridium-192	13.5 Gy x 2 implants 9.5 Gy BID x 2 implants				
	Boost Brach				
LDR Iodine 125 Palladium 103 Cesium 131	110–115 Gy 90–100 Gy 85 Gy				
HDR Iridium-192	15 Gy x 1 fx 10.75 Gy x 2 fx				
EBRT + SBRT Boost	9.5 Gy x 2 fx for SBRT boost				

Is SBRT boost feasible?

- ❑ EBRT + 19/2 SBRT vs. HDR-BT 131 patients from IR to HR, there were no significant differences.
- ❑ Good outcome: 5-yr bcRFR was 94.1% with local control 98.7%.

Chen
UCSF IJROBP
2020

Wegener
PROMETHEUS
EUO 2024

…

Clinical Goal of modern treatment

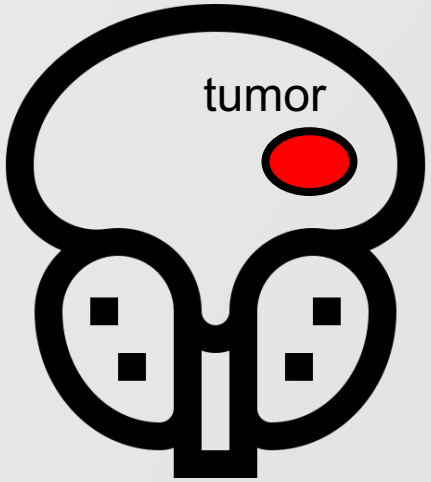
Local Primary

Conventional

Hypofractionated

EBRT ± BT boost

Focal Boost



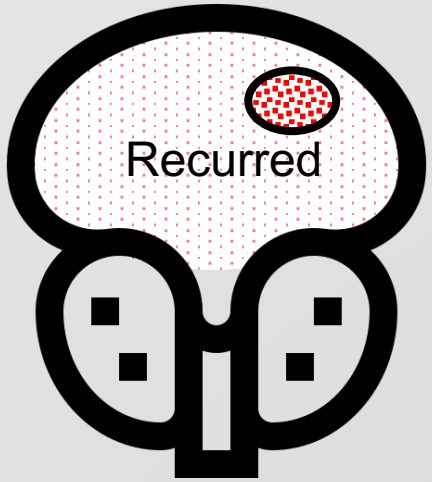
EBRT SIB

FLAME

DELINEATE

fBTsRT

Salvage Treatment



EBRT Salvage

GETUG, 2019 retro
MASTER, 2021 retro

HDR Salvage

****Fsharp**** **RTOG0526**

Brachytherapy Salvage Boost

Salvage treatment Whole gland

RTOG0526

Monotherapy-like
22Gy in 2 fx

Salvage treatment Focal region

MSKCC

Fsharp

Approaching treatment options

- **Evidence-based with *clinical trials* and outcome**
  - OS, PFS, bcPFR, toxicity, QoL…
  - Follow up range (>5 years?)
  - Limitations (patient cohort, study design, control variable …)

- **Institutional experience-based**
  - Phyisicist team → commissioning, QA
  - Physician team → skill, preference, belief
  - *Profit-driven → favoring hyperfractionation*.

Approaching treatment options

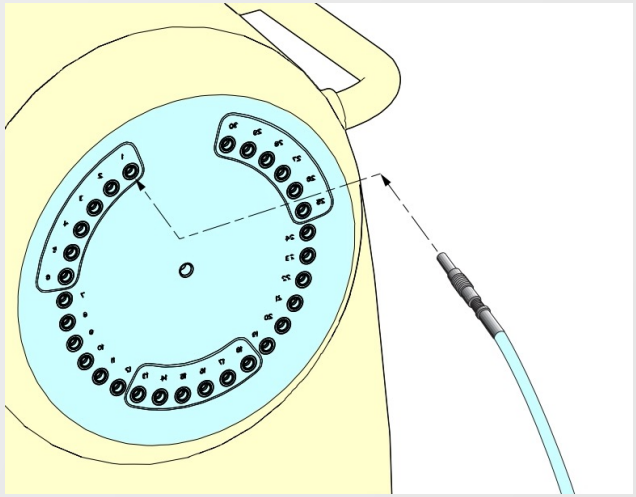
A comprehensive evaluation of efficacy, toxicity, symptoms, technical difficulty, preference is very institutional dependent!

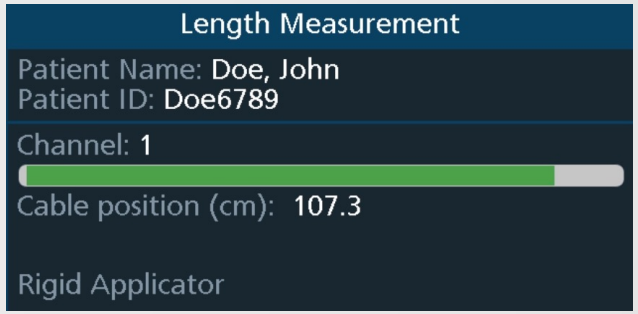
brief introduction: high-dose-rate (HDR)

Afterloader

>12 Gy/h

Transfer Tube Guide

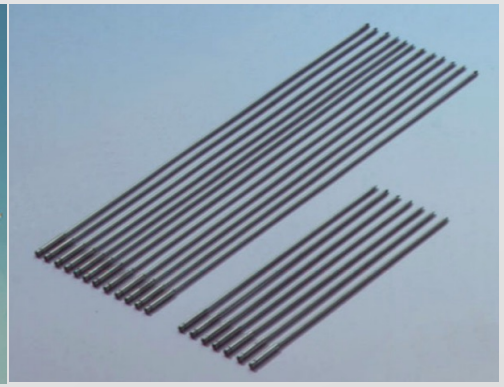




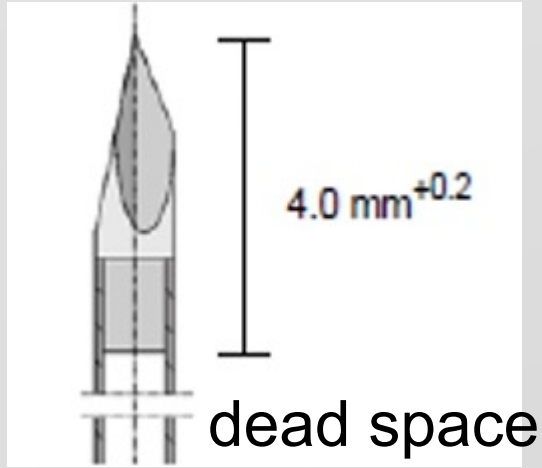
Total Length = 150 cm

SS needles

Ti needles



Catheters w stylets



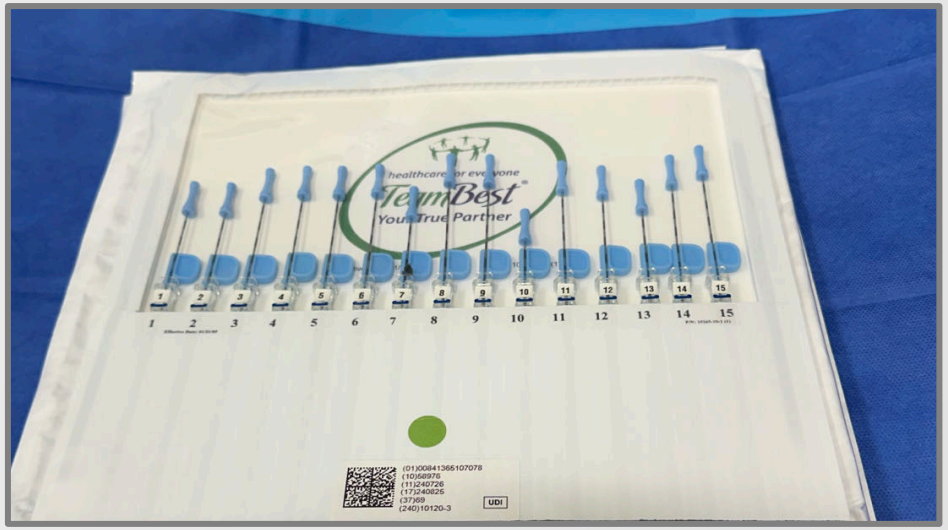
dead space

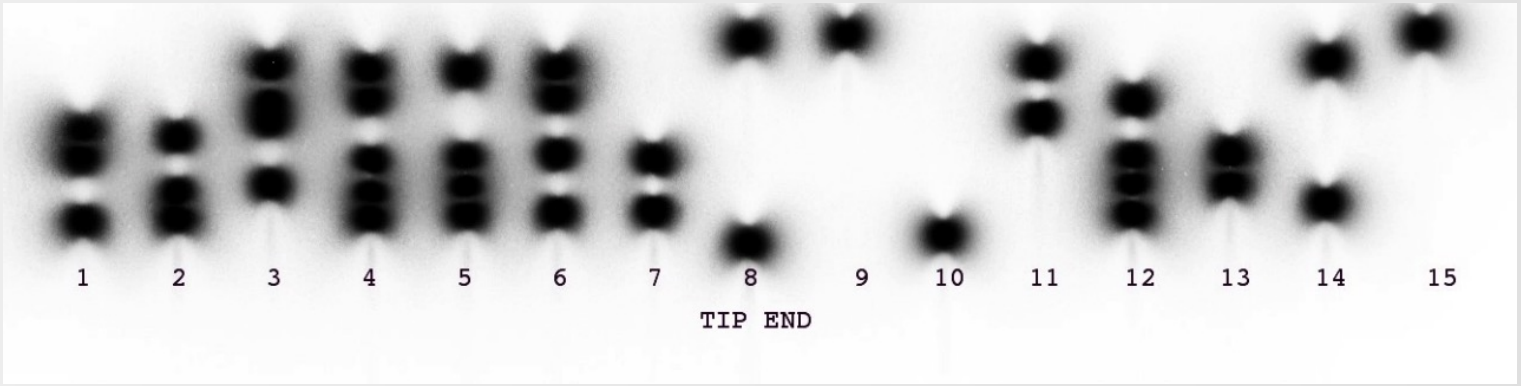
brief introduction: Low-dose-rate (LDR)

seeds

<2Gy/h

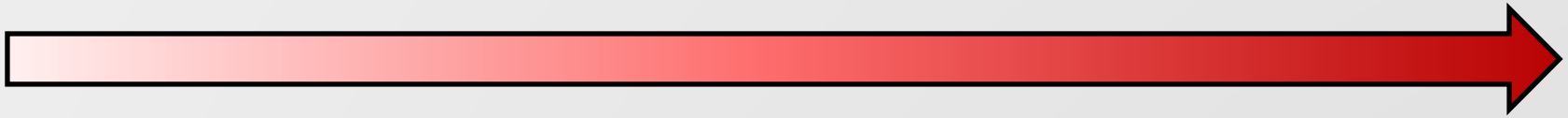
Preloaded needles





Film for positional verification

Brachytherapy Clinical Guideline



ABS

Low risk	Intermediate risk	High risk
HDR or LDR mono	HDR mono, EBRT + LDR boost	EBRT + HDR boost + ADT*

RWJ

Low risk,	Intermediate risk		High risk
	Favorable	Unfavorable	
HDR Monotherpy 13.5 cGy x 2		EBRT + HDR boost ± ADT 45 Gy in 25 EBRT + 15 Gy x 1 BT	

“It is just what we treat with.”

Brachytherapy Clinical Guideline

RWJ

Low risk,	Intermediate risk		High risk
	Favorable	Unfavorable	
HDR Monotherpy 13.5 cGy x 2		EBRT + HDR boost ± ADT 45 Gy in 25 EBRT + 15 Gy x 1 BT	

- **Why 13.5 cGy × 2 for mono?**
  - **Morton RTO Sunnybrook trial**
  - **Demanes BT 2014**
- **Why 15 cGy × 1 for boost?**
  - **RTOG 0924, RTOG 1115**
  - **UCSF, Toronto practice and Martell et al.**

HDR vs LDR: Is HDR favored?

evidence

toxicity

“They have similar outcomes.
Toxicity is so much better!
Patient heals soon.”

Hideya et al.
Moidene ASTRO
Hathout et al.

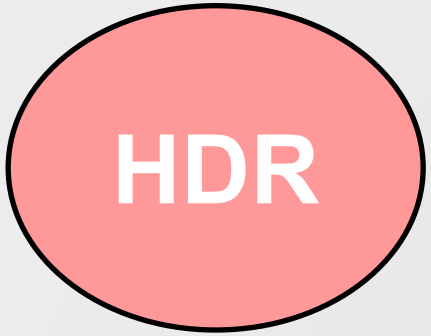
Preference

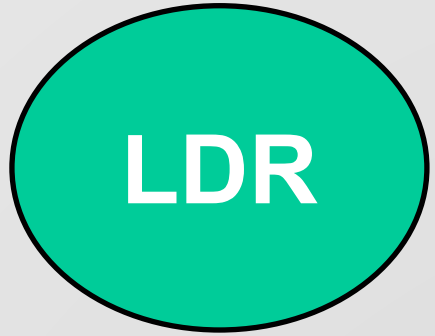
“LDR?? Ew!!
(LDR) This is exciting!
Patient preferred LDR!
… ess exposure!”

Technical

“Patient has implants.
If seeds move, …”

HDR vs LDR: a biophysical perspective





equivalently higher dose per fraction and increase biological cell kill for late reacting tumors

redistribution of cells into radiosensitive phase of cell cycle, reoxygenation, and repair of normal tissues

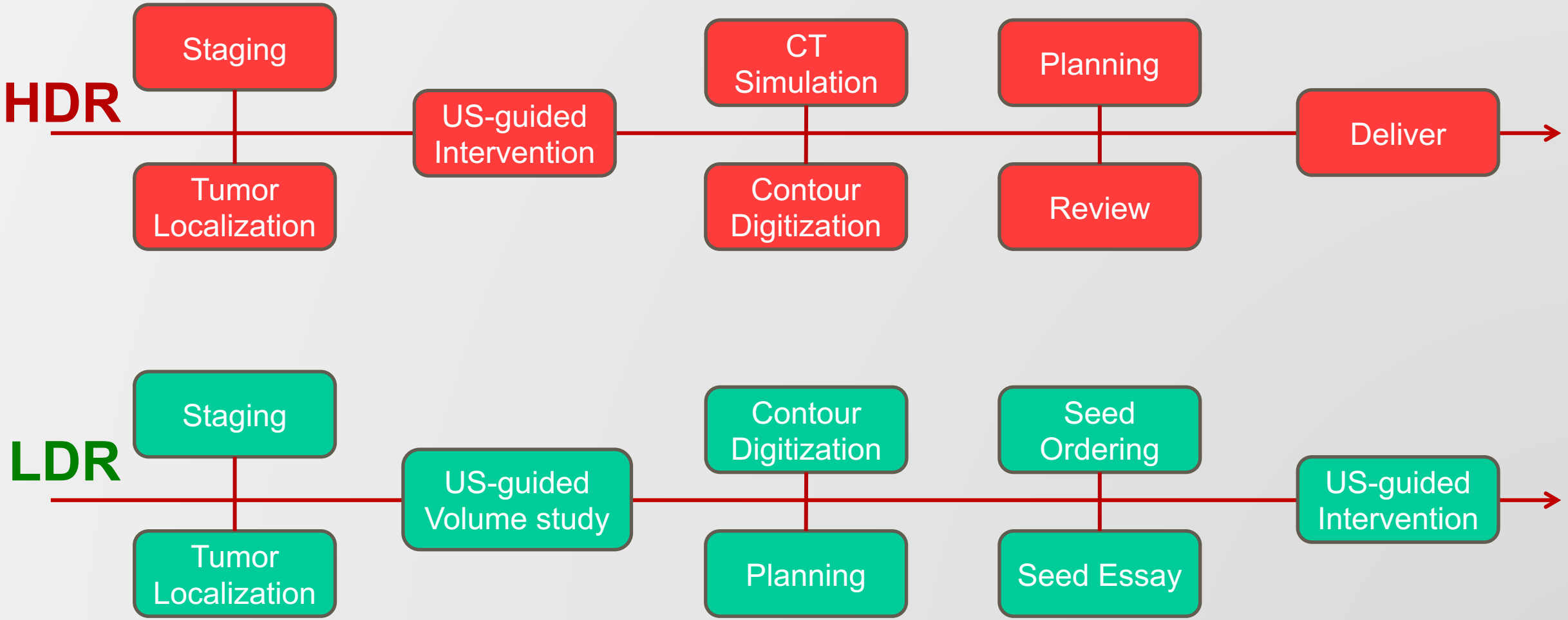
HDR vs LDR: a final word

Sufficient clinical data?
with sufficient follow up?

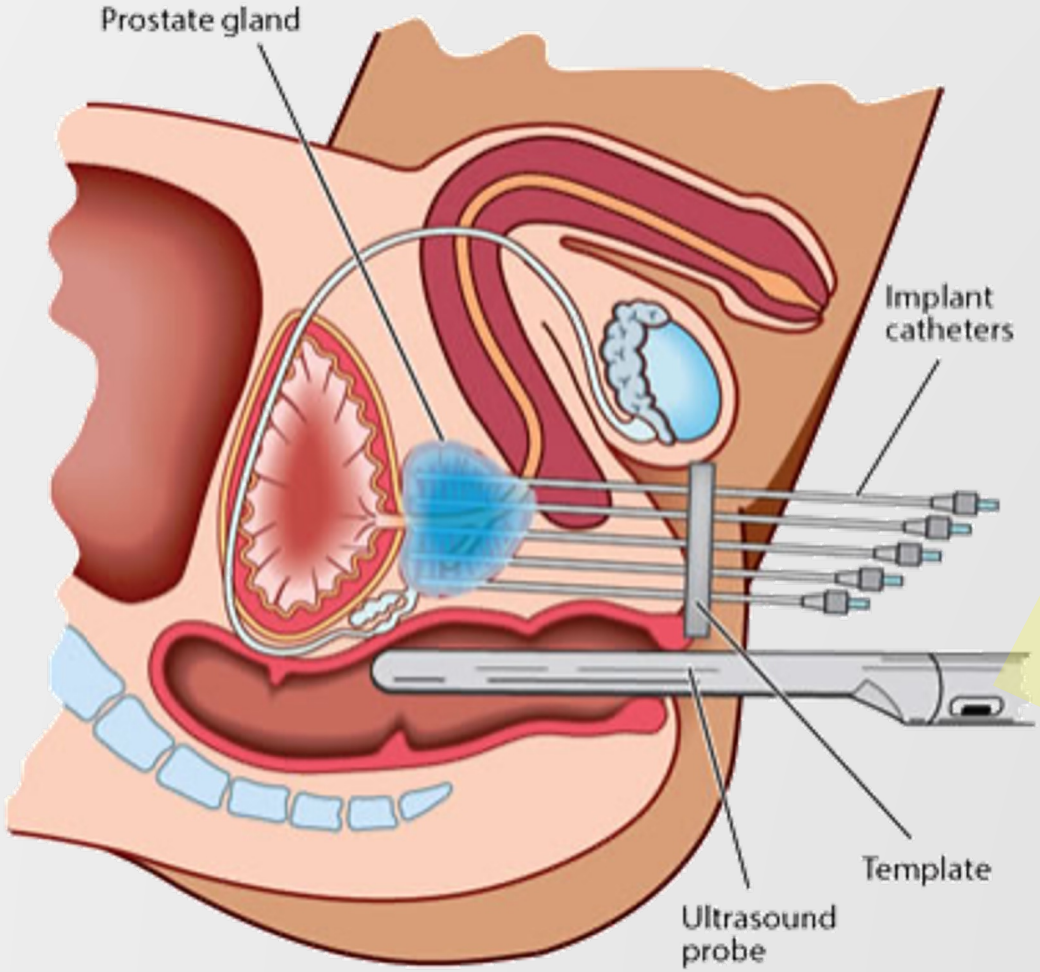
Seed Selection

Isotope	$T_{1/2}$ [days]	90% dose [days]	Energy [keV]	Initial dose rate (cGy/hr)	Seed activity (mCi)	Dose [Gy]	
						Mono	Boost
^{192}Ir	74	-	372*	450	**10,000**	**27, 19**	15
^{125}I	60	197	28	7.0	**0.16-1.00**	140-160 (140)	108-110
^{103}Pd	17	56	22	19.6	0.50-1.90	110-125	90-100
^{131}Cs	10	33	30.4	34.4		100-115	85

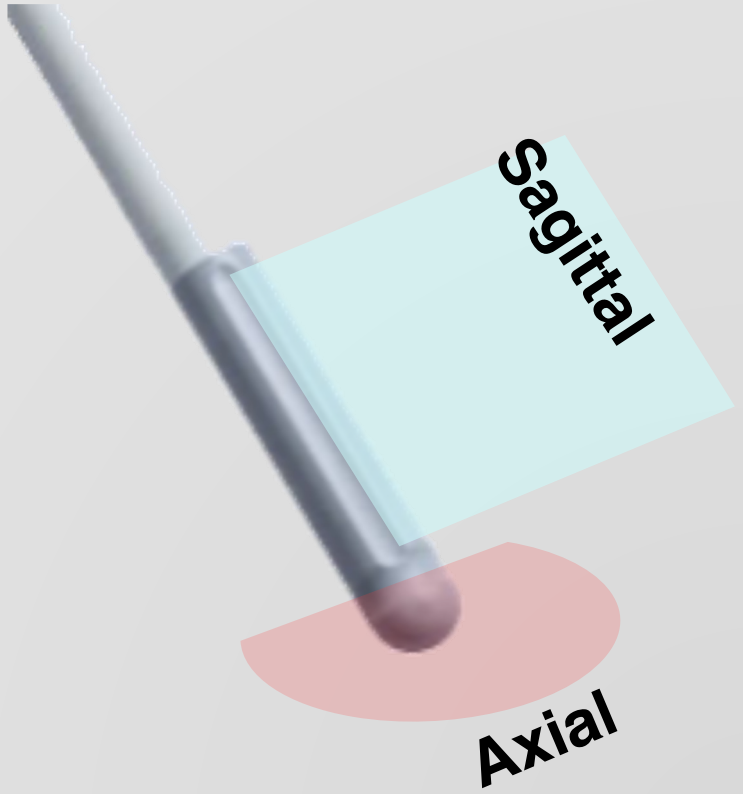
Imaging-guided prostate BT workflow



Transrecal ultrasound (TRUS) guidance



E14CL4b (9048)
Endocavity Biplane Transducer



TRUS guidance

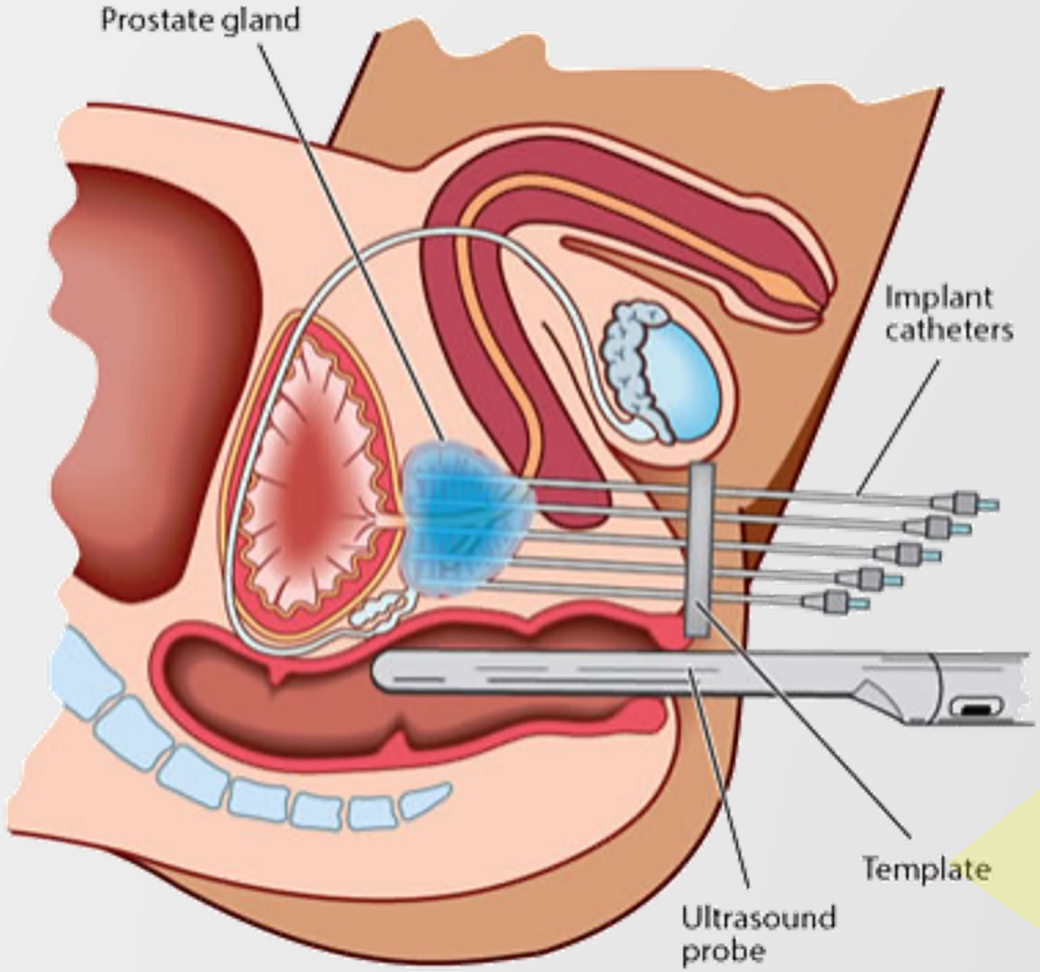
- Reliable
- Efficient
- Affected by prostate size

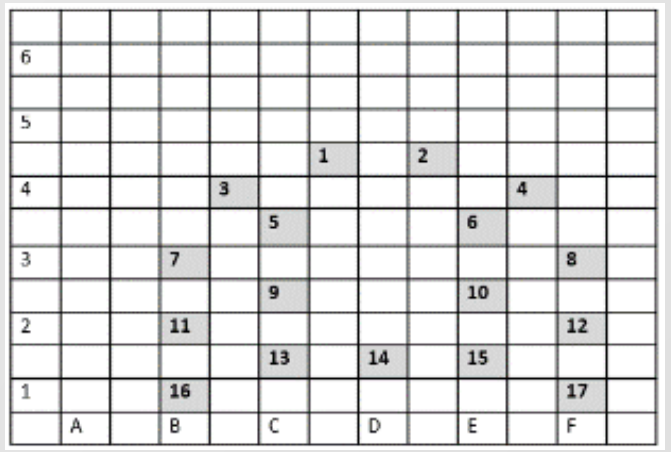
Template-based

VS

Free-hand

- Fexlible
- Not efficient

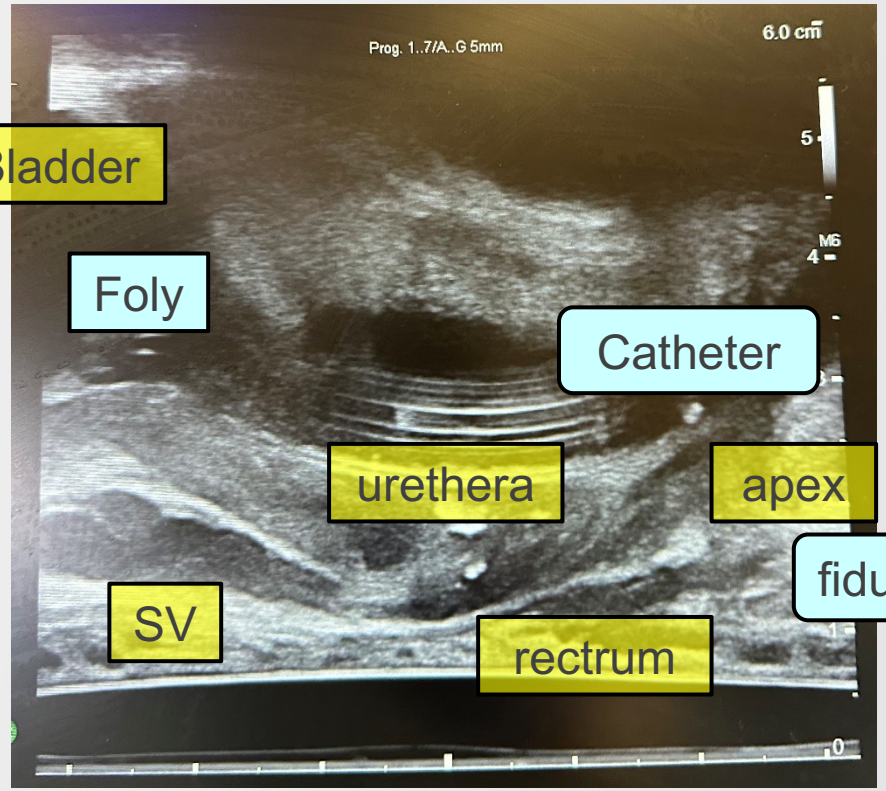




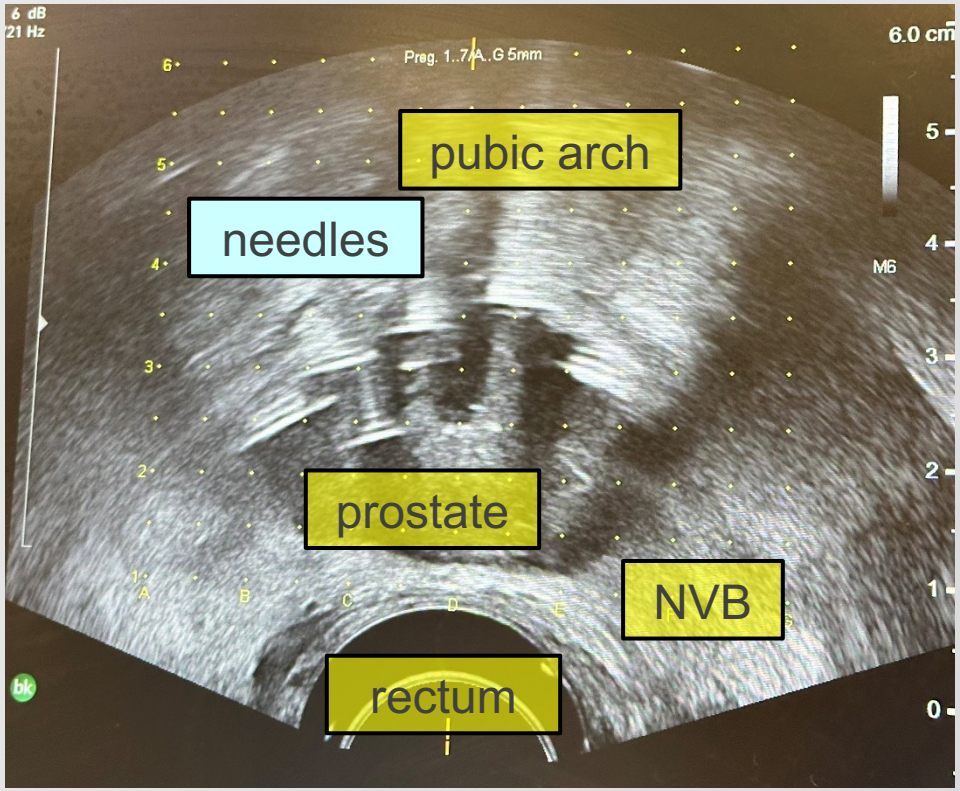
Cook template

TRUS guidance

Transverse view - stepping



Sagittal view - Rolling



Foley Catheter

silicone

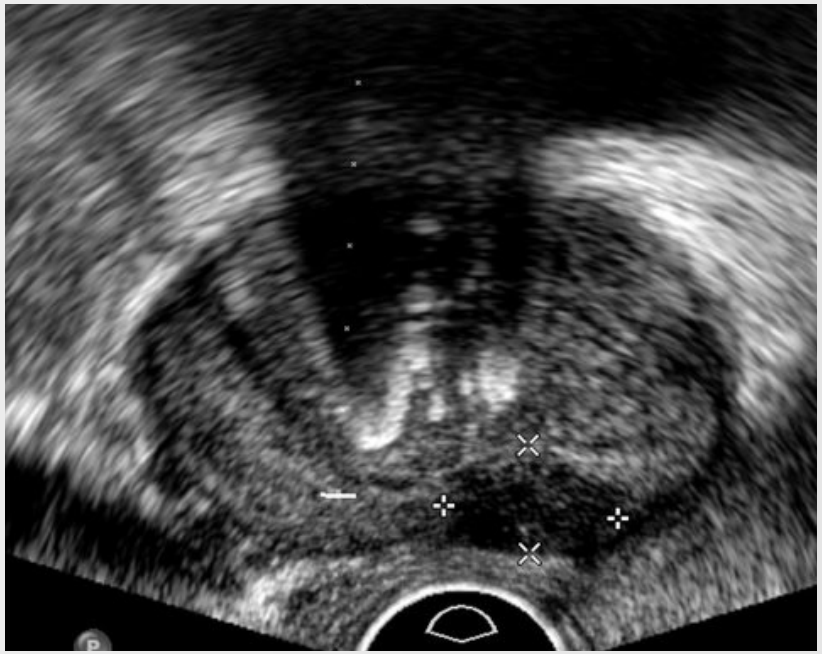
latex

needles

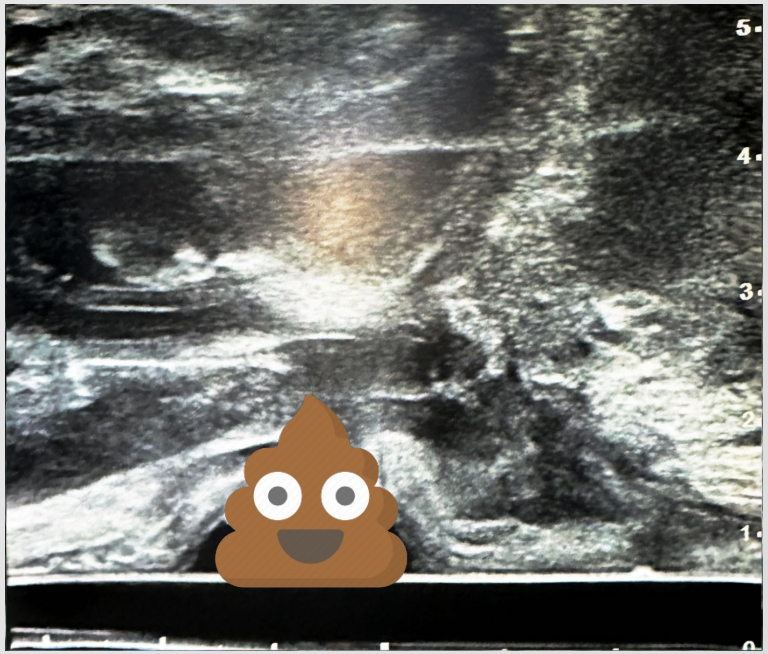
titanium

SS

Well … annoying



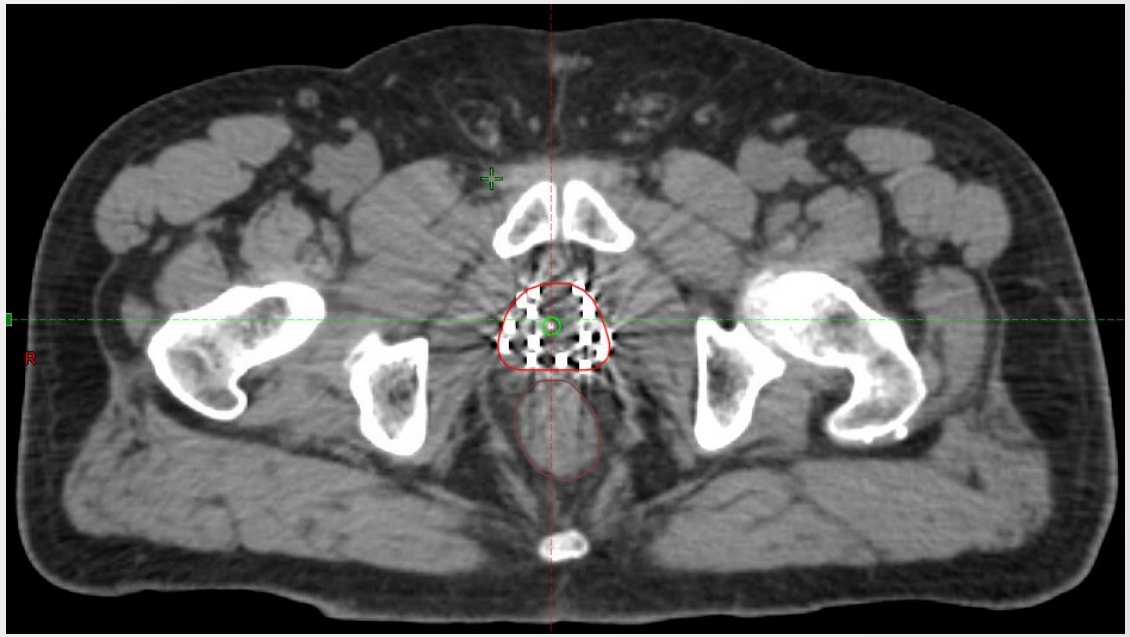
Calcification



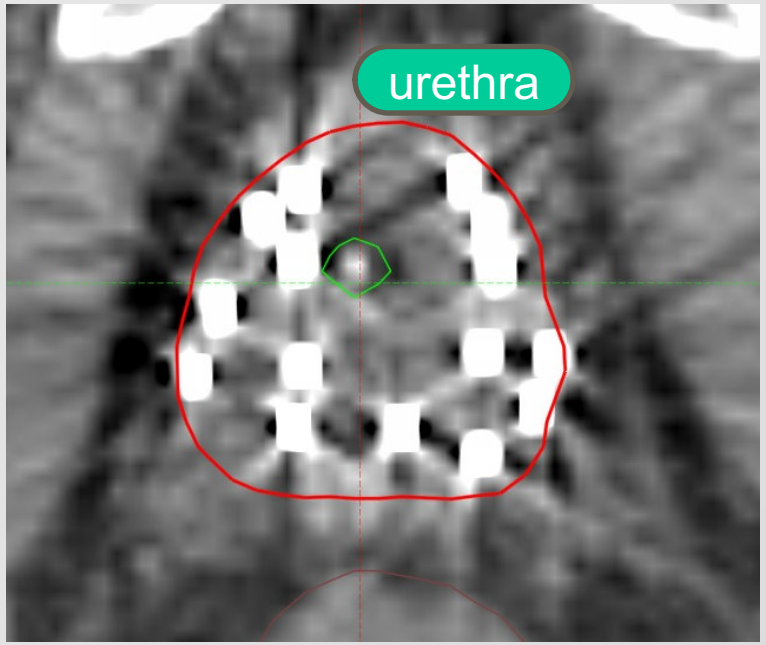
Air gap

Planning CT for HDR

Post-implant CT



zoomed-in



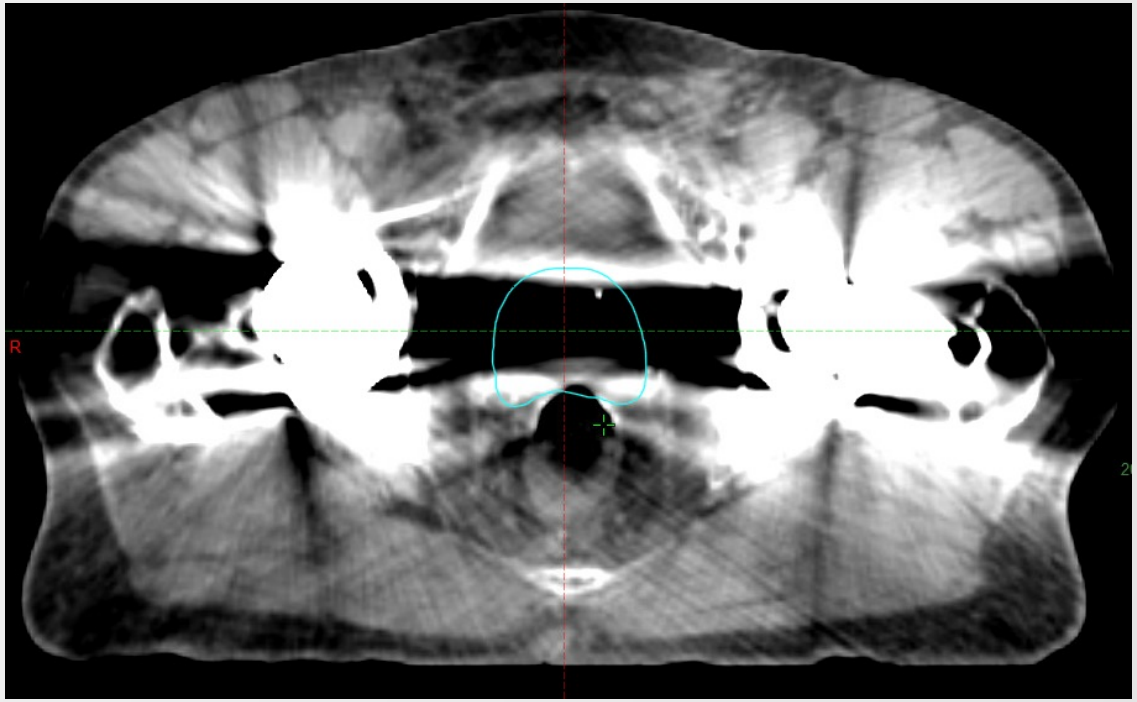
Assume Water

Metal artifact

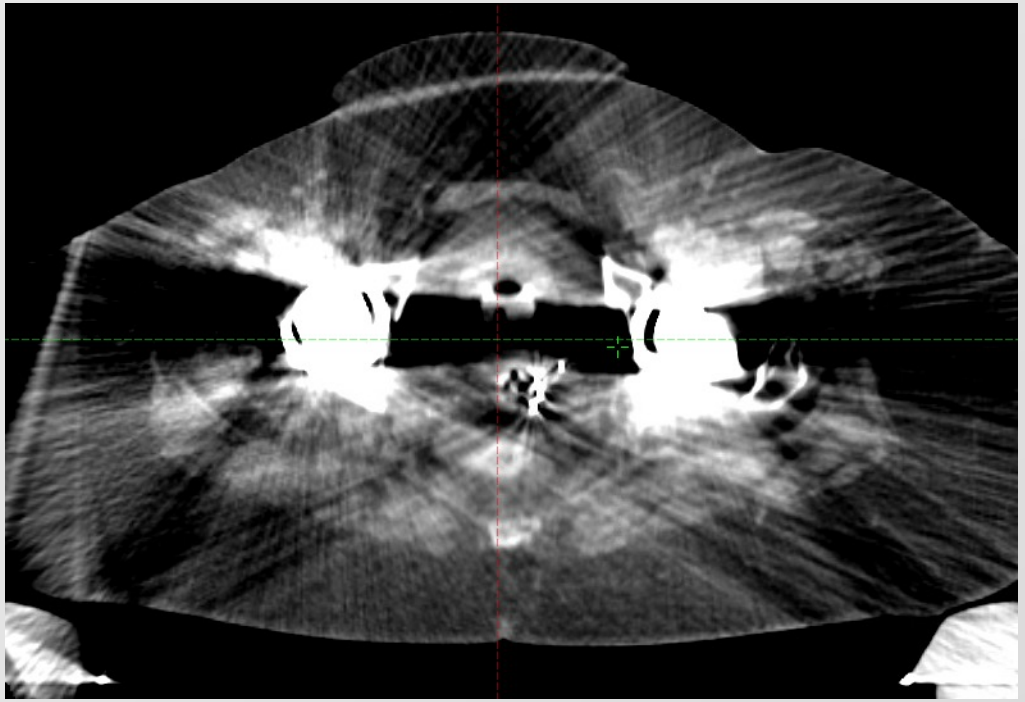
Latex/Sil Catheter

Well… prosthetic implant

Prostate cancer with prosthetic implant



Endometrium Cancer w vaginal cuff recurrence

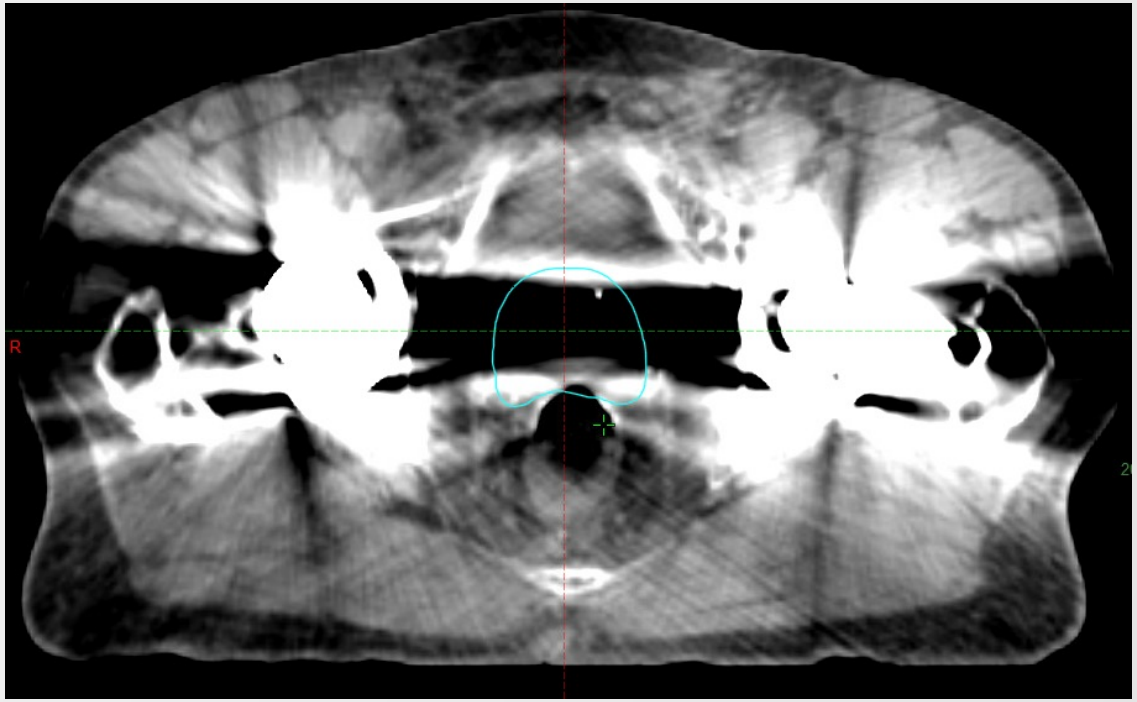


Solution

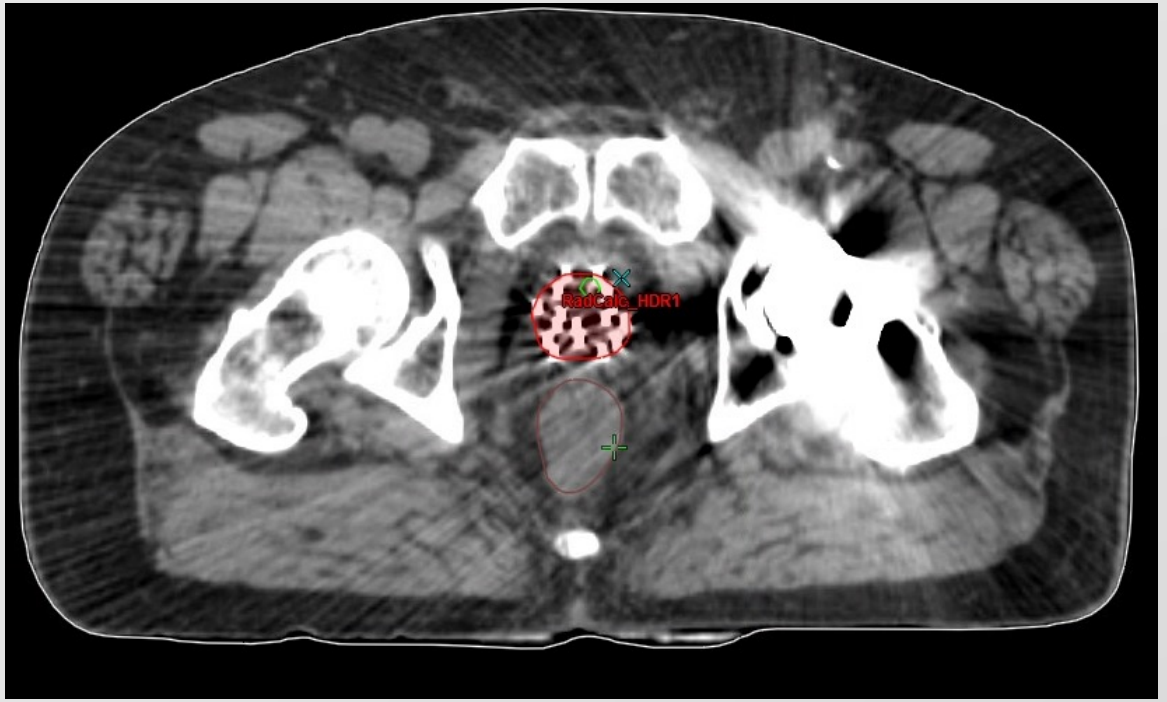
- Metal artifact reduction
- Fiducial
- US-guided
- LDR

Well… prosthetic implant

Prostate cancer with prosthetic implant



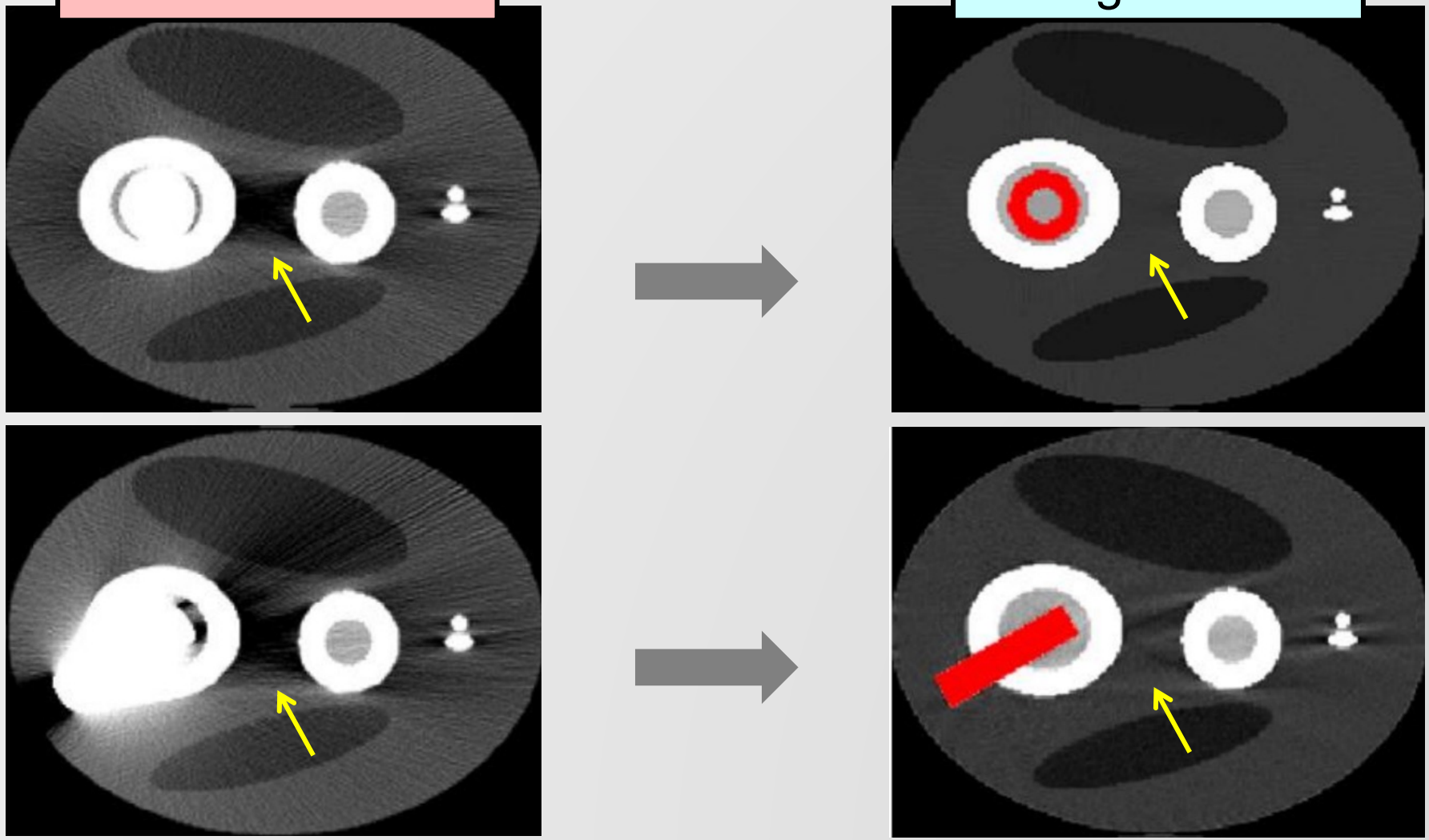
Prostate cancer with prosthetic implant (II)



CT Physics Explanation

Metal Implants induced artifacts

Metal Reduction Algorithm

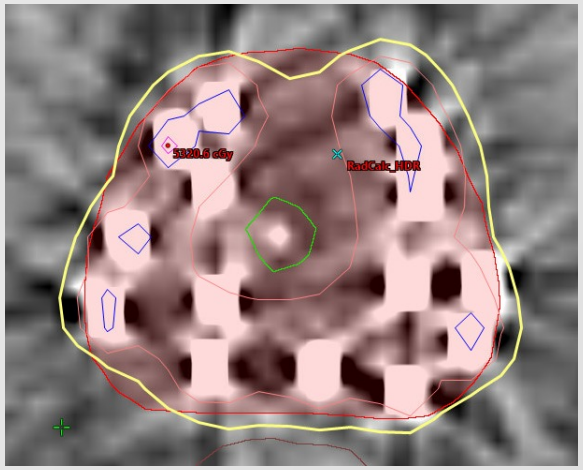


Treatment Planning

Dosimetric Goal

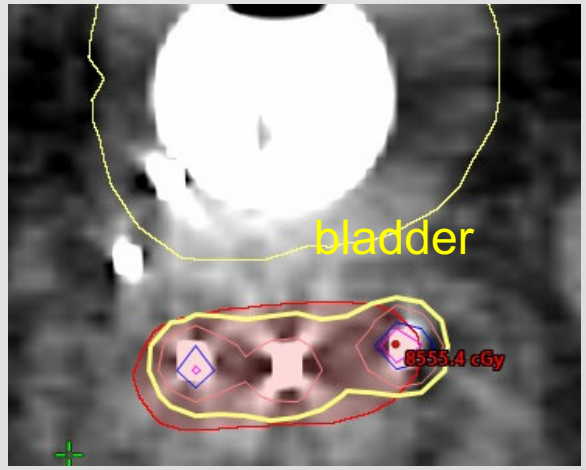
Organ	Clinical Goal
Prostate	D 90.0 % ≥ 105.0 %
	V 100.0 % ≥ 95.0 %
	V 150.0 % ≥ 35.0 %
	V 200.0 % ≥ 12.0 %
Bladder	D 1.0 cm³ ≤ 75.0 %
Rectum	D 0.1 cm³ ≤ 75.0 %
	D 0.1 cm³ ≤ 100.0 %
Urethra	**D 10.0 % ≤ 120.0 %**
	Dmax ≤ 125.0 %
	D 0.1 cm³ ≤ 1950 cGy

Evaluation



Rectum

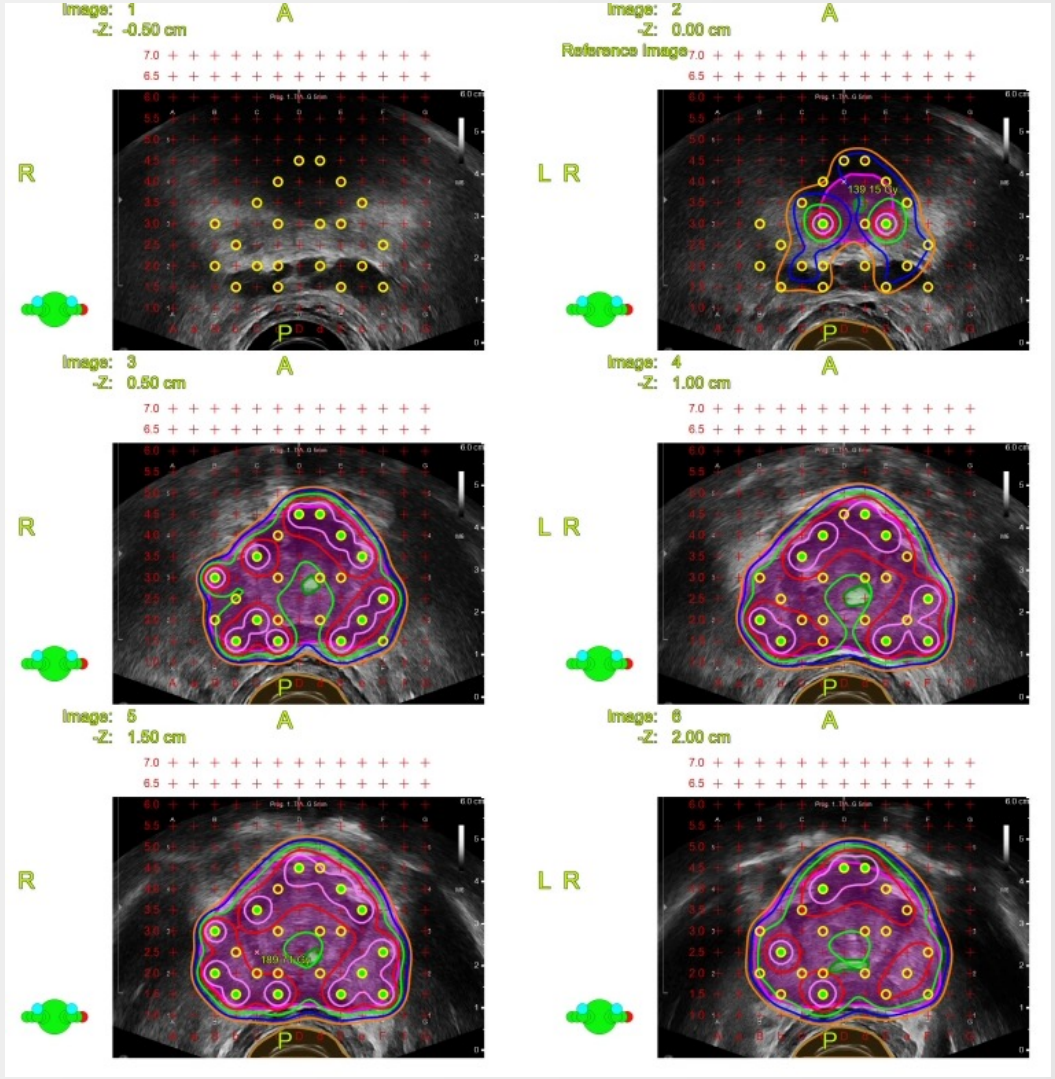
- V100% Coverage
- Urethra sparing
- Hot spot (fibrosis)



SV

- Where is the tumor?
- NVB sparing?
- Inclusion of SV?

LDR procedure: Volume Study

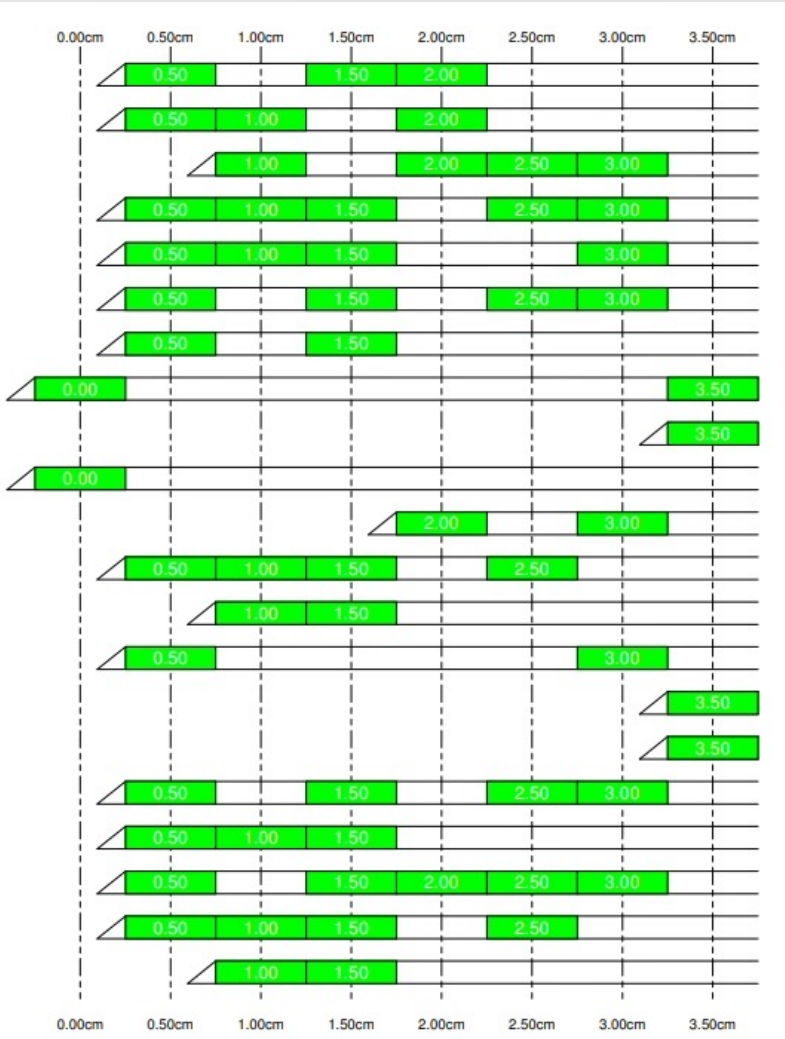


Prostate is contoured in 5 mm increments from the base to apex

VariSeed Software

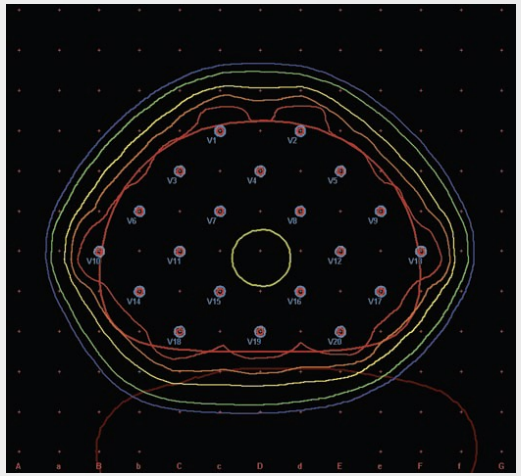
Needle Number	Retraction (cm)	Hole Location	Number Seeds
1	0.50	D4.5	3
2	0.50	d4.5	3
3	1.00	c4.0	4
4	0.50	E4.0	5
5	0.50	C3.5	4
6	0.50	e3.5	4
7	0.50	B3.0	2
8	0.00	c3.0	2
9	3.50	d3.0	1
10	0.00	E3.0	1
11	2.00	b2.5	2
12	0.50	F2.5	4
13	1.00	B2.0	2
14	0.50	C2.0	2
15	3.50	c2.0	1
16	3.50	d2.0	1
17	0.50	e2.0	4
18	0.50	b1.5	3
19	0.50	c1.5	5
20	0.50	E1.5	4
21	1.00	F1.5	2

= Special loading

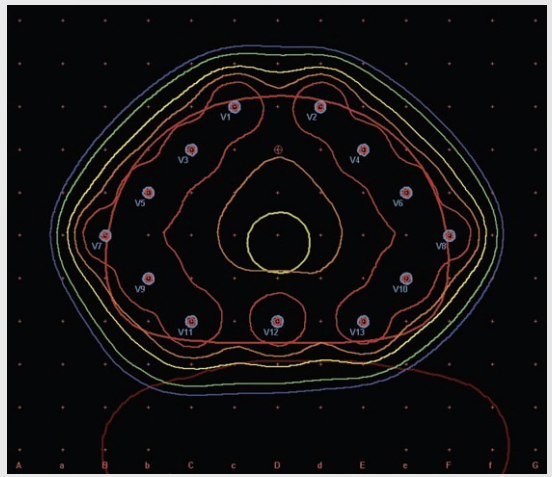


LDR procedure: seed loading

Uniform Loading



Modified uniform loading

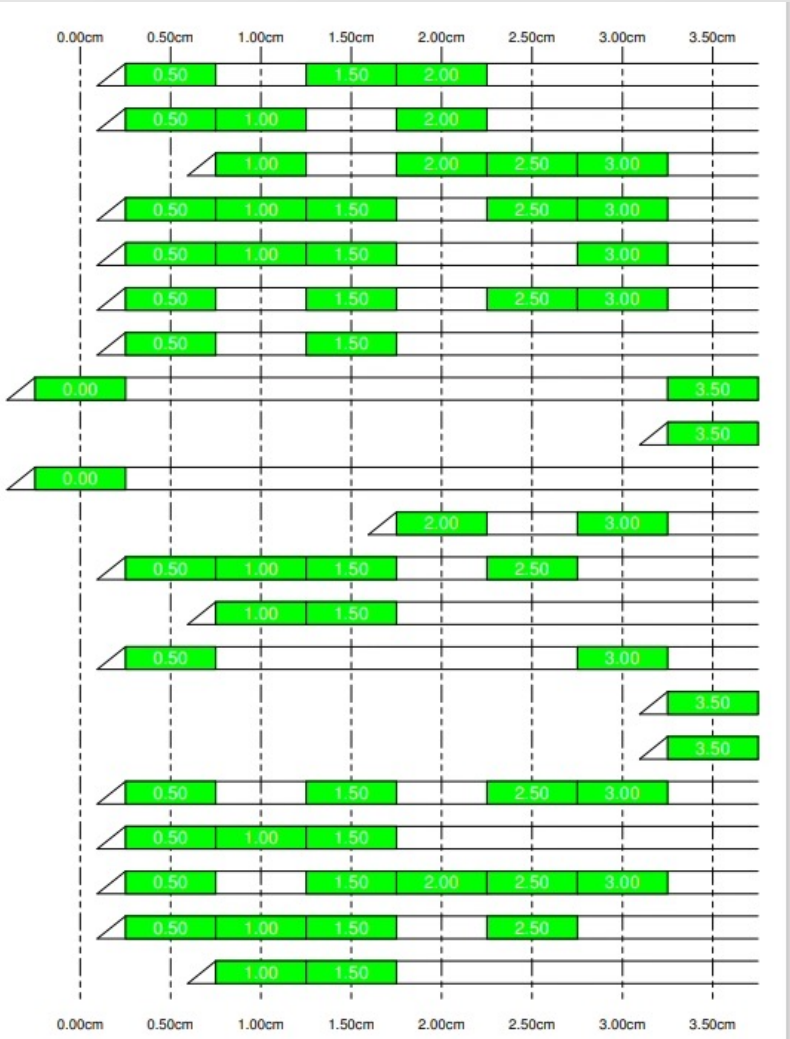


① Seed Number

Needle Number	Retraction (cm)	Hole Location	Number Seeds
1	0.50	D4.5	3
2	0.50	d4.5	3
3	1.00	c4.0	4
4	0.50	E4.0	5
5	0.50	C3.5	4
6	0.50	e3.5	4
7	0.50	B3.0	2
8	0.00	c3.0	2
9	3.50	d3.0	1
10	0.00	E3.0	1
11	2.00	b2.5	2
12	0.50	F2.5	4
13	1.00	B2.0	2
14	0.50	C2.0	2
15	3.50	c2.0	1
16	3.50	d2.0	1
17	0.50	e2.0	4
18	0.50	b1.5	3
19	0.50	c1.5	5
20	0.50	E1.5	4
21	1.00	F1.5	2

= Special loading

② Position of the 1st Seed



Physics responsibility

- Seed ordering (understand shipping labels)
- Seed Essay (TG-56)
- Seed disposal – tweezer and small lead pig.
- GM counter and survey meter for patient and room survey to ensure no loose seed
- Patient release (NUREG 1556)
- Postimplant dosimetric evaluation (TG137)

Discussion

- Metastatic (+recurred) prostate cancer not covered in this presentation. STOMP, ORIOLE; KNIGHT, INDICATE
- Xofigo (Ra-223) for bone mets. RAVENS
- Pluvicto targets (Lu-177) PSMA. VISION
- Radiogenomics potentials for prognostic values.

Contact: cz453@cinj.Rutgers.edu

Prostate cases

Case No.	Prostate Size	Risk	Imaging	Biopsy	PSA
1	29.88cc	Intermediate unfavorable risk	left apical anterior peripheral zone PI-RADS 4	5 positive	Elevated
2	51.74 cc	Intermediate unfavorable risk	bilateral apical, mid anteria PI-RADS 5	>6 positive	14.4
3	32.6 cc	High risk	Left apex – base, peripheral zone, PI-RADS 5		
4					
5					
6					
7					
8					